Original Article

Drug-drug interactions in prescriptions for hospitalized elderly with Acute Coronary Syndrome

Tiago Aparecido Maschio de Lima[1], Moacir Fernandes de Godoy[2]

[1] Pharmacist, Master in Nursing. Clinical Research Coordinator at the Hospital de Base da Faculdade de Medicina de São José do Rio Preto. Professor at União das Faculdades dos Grandes Lagos. São José do Rio Preto, SP, Brazil. E-mail: tiagomaschio.farmacip@gmail.com.

[2] Physician, Ph.D. in Cardiovascular Surgery. Adjunct Professor at the Faculdade de Medicina São José do Rio Preto. São José do Rio Preto, SP, Brazil. E-mail: mf60204@gmail.com.

Received: 08/12/2016.
Accepted: 05/18/2017.
Published: 10/01/2017.

Suggest citation:
Lima TAM, Godoy MF. Drug-drug interactions in prescriptions for hospitalized elderly with Acute Coronary Syndrome. Rev. Eletr. Enf. [Internet]. 2017 [cited __/__/__];19:a24. Available from: http://dx.doi.org/10.5216/ree.v19.42764.

ABSTRACT

The objective was to determine the rate of potential drug-drug interactions in prescriptions for elderly diagnosed with Acute Coronary Syndrome in a teaching hospital. This is an exploratory, descriptive study that analyzed 607 prescriptions through databases to identify and classify the interactions based on intensity (major, moderate or minor), the mechanism (pharmacokinetic or pharmacodynamics) and documentation relevance. We detected 10,162 drug-drug interactions, distributed in 554 types of different combinations within the prescribed drugs, and 99% of prescriptions presented at least one and a maximum of 53 interactions; highlighting the prevalence of major and moderates ones. There was a correlation between the number of drug-drug interactions and the number of prescribed drugs and the hospitalization time. This study contributes for the delimitation of a prevalence pattern in drug-drug interactions in prescriptions for Acute Coronary Syndrome, besides subsidizing the importance of the effective implementation of the Clinical Pharmacy in teaching hospitals.

Descriptors: Drug Prescriptions; Aged; Cardiology; Drug Interactions; Hospitals, Teaching.

INTRODUCTION

Seniors with Acute Coronary Syndrome (ACS) is submitted to use the polypharmacy that configures the use of drugs from different therapeutic classes, especially when they are affected by concomitant diseases, cardiovascular or not, which are common for this age group. The polypharmacy can cause risk of drug-drug interactions which, in the clinical practice represent serious problems, besides causing serious

adverse events, resulting in drug therapy inefficacy[1].

Drug-Drug Interaction (DDI) is a pharmacological or clinical answer to the concomitant administration of two or more drugs that are divergent from the response caused by these drugs when used alone. We classify them according to the mechanism as pharmacokinetics in a situation when changes occur in the concentration of at least one of the drugs involved in the interaction during the processes of absorptions, distribution, biotransformation, or elimination. While pharmacodynamics interactions are related to the action mechanism of the involved drugs, typically through antagonism or synergism. The expression "Potential Drug-Drug Interactions" (PDDI) describes interactions between drugs from a previously known and documented medical prescription, but they can occur or not, requiring clinical and laboratory monitoring[2-3].

The knowledge of the main pharmacological DDI characteristics contributes to its clinical management. Therefore, it is fundamental to prevent adverse events provoked by the presence of DDI in medical prescriptions, through the access to databases with detailed information about DDI mechanisms, intensity classification, management guidance and associated risks[1,4-5].

The clinical data collection and the DDI identification are activities developed by clinical pharmacists, as well as, other drug-related problems, monitoring, and patient management, contributing to the medical team to deal with necessary clinical interventions, improving the pharmacotherapy quality. Therefore, it minimizes risks from unfavorable results arising from the drug therapy, besides the decrease in costs[6-8].

Considering that DDI configures within the factors responsible for health and pharmacoeconomic losses, our objective was to determine the rate and the characteristics of PDDI in prescriptions for elderly hospitalized with the ACS diagnosis. We chose this patient profile due to the consumption of drugs from diverse pharmacological groups for the treatment of ACS and the frequent concomitant diseases[1,7].

METHODS

We conducted an exploratory, descriptive study. We analyzed 607 prescriptions from 119 patients diagnosed with ACS attended by the Unified Health System, better known by the Acronym SUS. The patients attended a Cardiology Clinic, from a teaching hospital in the inner state of São Paulo, Brazil. We conducted the study between April and July of 2014. Patients who were 60 or more years old, independently of sex, were included in the study. We analyzed the prescriptions of each patient included during the hospitalization period in the unit.

The study hospital is a reference for ACS in the city and its surroundings. The fact that the hospital is linked to a teaching institution and, that it has a medical residency program increases the importance of prescriptions' analyses by the clinical pharmacist. However, there is no exclusive pharmacist's team yet for the clinical activities, and the Clinical Pharmacy is in its beginning stages.

For the PDDI assessment and classification, we used the databases Micromedex[9], Drugs[10] and, Medscape[11]. We classified PDDI according to their intensity level as:

Major, contraindication, important or serious (when the interaction represents risk to life and/or request medical intervention to decrease or avoid serious effects, or the drugs are contraindicated for concomitant use);

Moderate or significant (when the interaction exacerbates the patient's health problem and/or requires a pharmacotherapy change);

Minor or secondary (when the interaction results in limited clinical effects. The manifestations can include an increase in the frequency or intensity of adverse effects, but generally, they do not require a major pharmacotherapy change) [9-11].

The Micromedex database is evidence-based and broadly used in many countries. The Drugs and Medscape databases were included in this study due to its free online availability, becoming important sources of public health information[4-5,9-11]. In the case of disagreements of classifications in the databases, we considered the major intensity. We also classified PDDI by its pharmacokinetic or pharmacodynamic profiles. In the PDDI analysis, we also included the interactions considered positives or intentional, which are those that propitiate benefits through its synergic effect. We excluded phytotherapy, electrolytes from the serum therapy, and diet components[4-5].

Also, we classified interactions according to documentation relevance as:

- Excellent (in cases where controlled studies established the interaction existence);
- Good (in cases where the documentation vehement suggest the presence of the interaction but lacks controlled studies adequately conducted);
- Fair (when the available documentation is unsatisfactory, but the pharmacological considerations lead the clinicians to suspect of an interaction existence, or the documentation is good for a drug pharmacologically similar);or
- Unknown[9].

We assessed the correlation between PDDI with age, the number of prescribed medications, and patient's admittance time, using the Pearson's correlation coefficient. We also promoted a descriptive analysis to characterize drug-drug interactions. We presented discrete and non-continuous variables as median, minimum and maximum interval. For the categorical variables, we presented them as absolute numbers and proportions (%). In all circumstances, we considered a $p<0.05$ value as statistically relevant. We used the SPSS Statistics version 22.0 to carry out the analyses.

The research was approved by the Ethics in Research Committee from Faculdade de Medicina de São José do Rio Preto (Famerp), under the registration nº 613.171. The ACS diagnosis was confirmed through participant's electronic records, and the consultation for medical prescriptions happened in the same manner.

RESULTS

All information referring to the analyzed prescriptions were entered in a Microsoft ® Excel (2010)

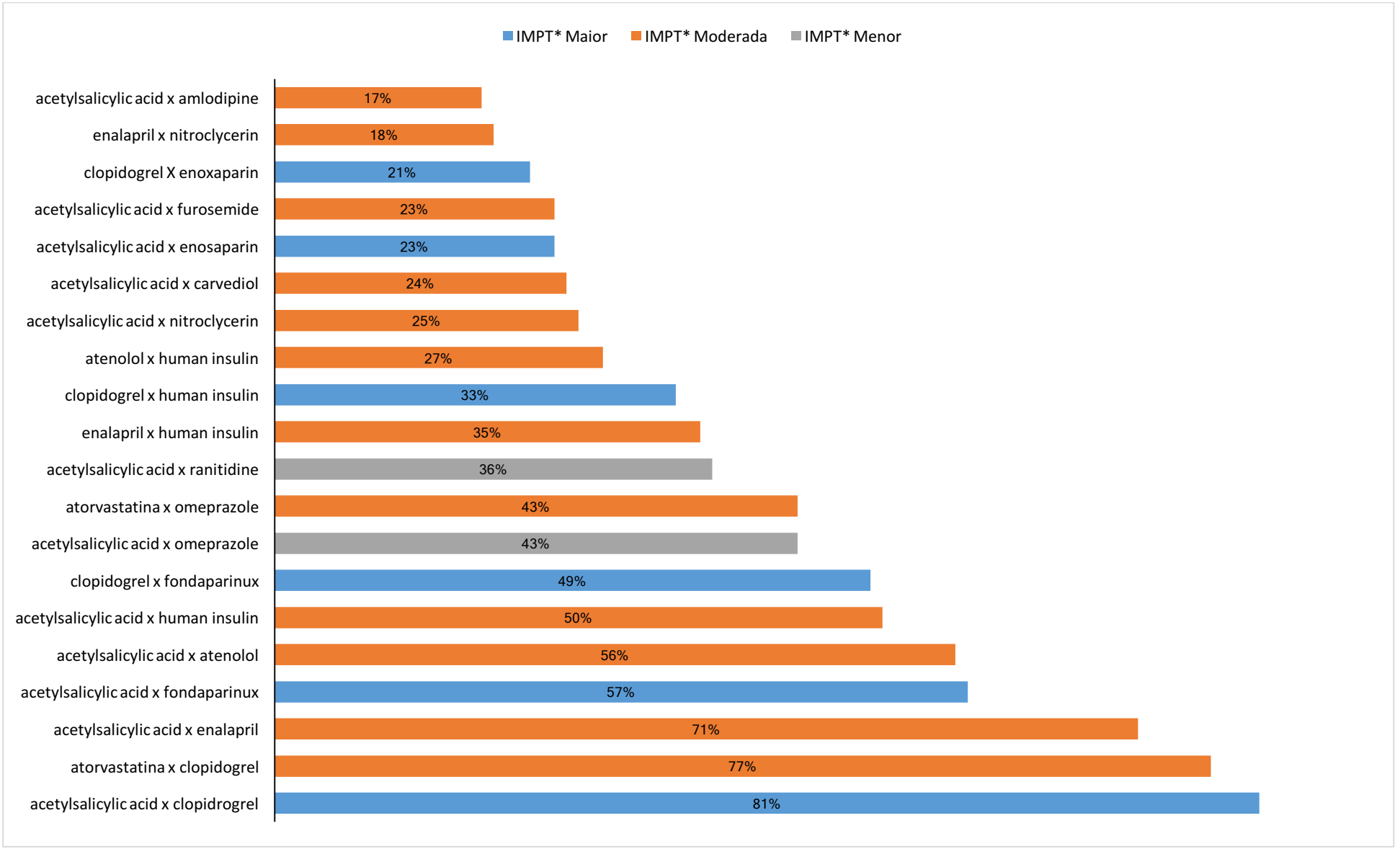
spreadsheet, regularly updated during the study through frequent consultation to the databases[9-11]. At the end of data collection, we updated and corrected the spreadsheet, counting with information from 145 different types of prescribed drugs, quantitative of 7,266 and a total of 10,162 PDDI related to these drugs, distributed in 554 types of various combinations of prescribed drugs. The median was 15, with a minimum of one and a maximum of 53 PDDI per prescription. Table 1 characterizes the categorical profile of PDDI observed in the prescriptions.

Table 1: Distribution per intensity level of the Potential Drug-Drug Interactions, São José do Rio Preto, SP, Brazil, 2014.

Intensity level	Total		Types of combination	
	n	%	n	%
Major	2,566	25	124	22
Moderate	6,504	64	372	68
Minor	1,092	11	58	10
Total	**10,162**	**100**	**544**	**100**

Among the analyzed prescriptions, 99% presented at least one PDDI, highlighting the prevalence of the moderate and major ones, 64% and 25%, respectively. Figure 1 shows the relationship of prescription percentages where we observed the 20 most frequent PDDI during the data analysis period. Regarding the interaction mechanism, we considered 73% of PDDI as pharmacodynamic and 27% as pharmacokinetic.

Table 2 lists main characteristics of the 14 major most observed PDDI. Table 3 presents the characteristics referring to the 14 most frequent moderate PDDI in the study.



*PDDI: Potentially drug-drug interactions

Figure 1: Prevalent types of PDDI in the study and its total frequency in the total of analyzed prescriptions, São José do Rio Preto, SP, Brazil, 2014.

Table 2: Characteristics and frequencies of the major PDDI prevalent in the studied prescriptions, São José do Rio Preto, SP, Brazil, 2014.

PDDI	Event	Probable General Mechanism	Databases*			Documentation	Frequency on prescriptions	
							n	%
Acetylsalicylic acid /clopidogrel	Increased risk of bleeding	Pharmacodynamic	1	2	3	Fair	493	81
Acetylsalicylic acid /fondaparinux	Increased risk of bleeding	Pharmacodynamic	1	2	3	Fair	344	57
Clopidogrel/fondaparinux	Increased risk of bleeding	Pharmacodynamic	1	2	3	Fair	298	49
Clopidogrel/omeprazole	Thrombosis risk due to the reduction of the clopidogrel active metabolite formation by the CYP2C19 inhibition	Pharmacokinetic	1	2	3	Excellent	200	33
Acetylsalicylic acid / enoxaparin	Increased risk of bleeding	Pharmacodynamic	1	2	3	Good	142	23
Clopidogrel/ enoxaparin	Increased risk of bleeding	Pharmacodynamic	1	2	3	Fair	125	21
Amlodipine /clopidogrel	Reduction of the antiplatelet effect and risk of thrombotic events	Pharmacokinetic	1	NC	NC	Excellent	84	14
Acetylsalicylic acid /heparin	Increased risk of bleeding	Pharmacodynamic	1	2	3	Fair	58	10
Clopidogrel/heparin	Increased risk of bleeding	Pharmacodynamic	1	2	3	Fair	38	6
Atorvastatin/clarithromycin	Risk of myopathy and rhabdomyolysis due to the increase in atorvastatin serum levels by the CYP3A4 enzymatic inhibition	Pharmacokinetic	1	2	3	Good	36	6
Clarithromycin /clopidogrel	Reduction in the clopidogrel active metabolite formation by the CYP3A4 inhibition, resulting in high platelet activity	Pharmacokinetic	NC	2	3	Not classified	35	6
Fondaparinux/levothyroxine	Increase in the foundaparinux effect	Pharmacodynamic	NC	NC	3	Not classified	33	5
Enalapril/spironolactone	Risk of hyperkalemia	Pharmacodynamic	1	2	3	Good	25	4
Acetylsalicylic acid/citalopram	Increased risk of bleeding	Pharmacodynamic	1	2	3	Good	24	4

* Databases: (1) Micromedex, (2) Drugs, (3) Medscape.

** NC: Not classified by the database.

Table 3: Characteristics and frequency of moderate PDDI prevalent in the studied prescriptions, São José do Rio Preto, SP, Brazil, 2014.

PDDI	Event	Probable mechanism	Databases*			Documentation	Frequency on prescriptions	
							n	%
Atorvastatin/clopidogrel	Reduction in the clopidogrel active metabolite formation by the CYP3A4 inhibition, resulting in high platelet activity	Pharmacokinetic	1	2	NC	Excellent	465	77
Acetylsalicylic acid /enalapril	Reduction of the anti-hypertensive effect	Pharmacodynamic	1	2	3	Excellent	430	71
Acetylsalicylic acid /atenolol	Reduction of the anti-hypertensive effect	Pharmacodynamic	1	2	3	Good	339	56
Acetylsalicylic acid /human insulin	Hypoglycemia risk	Pharmacodynamic	1	2	3	Fair	305	50
Atorvastatin/omeprazole	Risk of myopathy and rhabdomyolysis due to the increase in atorvastatin serum levels by the CYP3A4 enzymatic inhibition and P-glycoprotein	Pharmacokinetic	NC	2	NC	Not classified	262	43
Enalapril/human insulin	Hypoglycemia risk	Pharmacodynamic	1	2	3	Fair	215	35
Atenolol/human insulin	Hypoglycemia risk, hyperglycemia, and hypertension	Pharmacodynamic	1	2	NC	Good	165	27
Acetylsalicylic acid /nitroglycerin	Increase of the nitroglycerin serum level and addictive effect in the platelet depression	Pharmacodynamic	1	2	NC	Good	151	25
Acetylsalicylic acid /carvedilol	Reduction of the anti-hypertensive effect	Pharmacodynamic	1	2	3	Good	148	24
Acetylsalicylic acid /furosemide	Reduction of the anti-hypertensive effect	Pharmacodynamic	1	2	3	Good	138	23
Enalapril/nitroglycerin	Increase of the nitroglycerin hypotension effects	Pharmacodynamic	NC	2	NC	Not classified	109	18
Acetylsalicylic acid /amlodipine	Increase of the gastrointestinal bleeding risk and antagonism of the hypotension effect	Pharmacodynamic	1	2	NC	Good	102	17
Acetylsalicylic acid /losartan	Reduction of the anti-hypertensive effect and risk of kidney failure	Pharmacodynamic	1	2	3	Good	89	15
Enalapril/enoxaparin	Risk of hyperkalemia	Pharmacodynamic	NC	2	NC	Not classified	89	15

* Databases: (1) Micromedex, (2) Drugs, (3) Medscape

** NC: Not classified by databases

We observed a statistically significant positive correlation between the number of PDDI and hospitalization time (Table 4). We also highlight the positive correlation between the number of PDDI and the number of prescribed drugs (Table 4). There was no statistically significant correlation between the PDDI and participant's age (Table 4).

Table 4: Correlation between the number of the number of PDDI, total and per intensity, with participant's age, hospitalization time and the number of prescribed drugs, São José do Rio Preto, SP, Brazil, 2014.

	Total	Major	Moderate	Minor
	PDDI (119)**	PDDI (119)**	PTDI (118)**	PDDI (95)**
Age	r = 0.1523	r = 0.1728	r = 0.1377	r = 0.1444
	P= 0.0982	P= 0.0603	P= 0.1350	P= 0.1168
Days of hopitalization	r = **0.9045**	r = **0.9235**	r = **0.8769**	r = **0.7809**
	P= <0.0001	P= <0.0001	P= <0.0001	P= <0.0001
Number of drugs	r = **0.9719**	r = **0.9626**	r = **0.9510**	r = **0.8482**
	P= <0.0001	P= <0.0001	P= <0.0001	P= <0.0001

* r= Person's correlation coefficient; P= P-value; n = number of subjects (n=119).

** number of patients exposed to PDDI from the indicated class.

DISCUSSION

Our results allow us to evaluate the potential risks involving hospital prescriptions for ACS. It is known that due to the syndrome complexity and, by the large number of drugs used, and also considering the therapy used in its comorbidities, its prescriptions are more predisposed to present PDDI. These patients' profiles are also exposed to the occurrence of adverse events related to drugs, which is a fact associated with factors as the number of drugs administered, the complexity of therapeutic schemes, and the patient's clinical state. Still, it is important to highlight that pharmacotherapy prescription issues are widespread in teaching hospitals, reinforcing the importance of the clinical pharmacist for prescriptions' analyses[11-14].

The 99% parcel of prescriptions presenting at least one PDDI, the need to assess and to accompany prescriptions is evident, without neglecting the risks of potential interactions. The high PDDI number observed in our results corroborates with the rate obtained in other studies that point this common fact to cardiology prescriptions. Regardless of the relevance of this information to reinforce the potential risk inherent to PDDI, it is noteworthy that this number includes all PDDI classes, including also those considered intentional and positive for ACS pharmacotherapy[1,12-13].

The most frequent PDDI in this study was between acetylsalicylic acid and clopidogrel with a major intensity level. The guidance for clinical management of this interaction recommends the concomitant use of the two drugs should be cautious considering the continuing monitoring regarding the risk of bleeding. The same management recommendation is valid for all other larger interactions, detected in this study that involves the association between antiplatelet, as the acetylsalicylic acid and clopidogrel, and anticoagulant, as the enoxaparin and fondaparinux. National and International Clinical Protocols and Therapeutic Guidelines for ACS recommend the associate of these drugs and, although these interactions increase the risk of bleeding, those are also considered positive and intentional due to the proven benefit to reduce cardiovascular events in ACS patients[15-18].

Another most frequently PDDI found among the analyzed prescriptions was the interaction between the clopidogrel and omeprazole. The clopidogrel is a prodrug metabolized in the liver by the CYP2C19 to generate an active metabolite and to acquire its platelet antiaggregant properties. Omeprazole is an enzymatic inhibitor of the clopidogrel activating enzyme, provoking less effectiveness of the antiplatelet therapy due to the inhibition of the conversion in its active metabolite. Some studies were seen as controversial in the clopidogrel and omeprazole concomitant use. The recommendation is the counter-indication of their concomitant use. The recommended management is the omeprazole substitution by other proton pump inhibitor that does not act in the same cytochrome[19-21]. The drugs responsible for reducing the acidity, for example, antagonists of the H2 receptor, can lessen the incidence of gastrointestinal bleeding in ACS patients who are treated with antiplatelets and, at least if counter-indicated, its use should be considered. The use of a proton pump inhibitor is allowed, expect for the concomitant omeprazole or esomeprazole use with clopidogrel[2,15].

Within this context, all interactions which are more severe or moderate were notified to the medical team responsible for prescriptions, through specific interventions by verbal alerts. The posture adopted by the team facing warnings referred to PDDI corresponded to the recommended management orientations, especially referring to continuous monitoring due to risk of bleeding related to PDDI involving the association between antiplatelet and anticoagulant drugs, and the omeprazole substitution by ranitidine when associated to clopidogrel[2,15,19-21].

Moderate intensity PDDI is more common among drug-drug interactions, and consequently, they are configured between the most frequent in most studies assessing interactions present in prescriptions. In this study, moderate intensity interactions are noted involving anti-hypertensive drugs, and it can cause hypotension or reduction in the anti-hypertensive effect, and this last situation favors the ACS situation[9-11,16-18]. In these cases, the clinical drug should give the alert of potential interaction, and it can use the electronic record as a tool. Also, in partnership with the medical team, it can establish the conjunct decision of maintenance or change in the drug therapy, based in the patients' clinic and their laboratory results. In cases of plasmatic concentration changes caused by PDDI for some drugs, it is possible to verify their serum concentration through laboratory exams; therefore, observing if the interaction is effectively happening or not, but this routine involves costs and human resources and, it is not yet part of hospital routines, in most Brazilian hospitals, as well as, in the studied hospital[7,12-14,22].

The use of signaling interactions through alerts in the computerized records, the blockage of the electronic prescription in the presence of larger interactions and the daily drug intervention in partnership with the medical team, are effective strategies to reduce PDDI and its related issues[23-24].

Studies focused in the elucidation of risks and benefits of the drug therapy by the clinical pharmacist, as well as this study, represent a significant contribution to the tracking measures of adverse events to drugs and, the optimizing of the preconized drug therapy by clinical protocols. We recommend the use of at least three available sources in the literature for PDDI research, and the critical analysis of these available literature

sources, including the electronic databases, so a sub-identification does not occur. We suggest the implementation of the three databases used in this study. From the PDDI knowledge of each prescription, it is possible to identify the occurrence of real interactions through the accompaniment of visitors in the hospital room, the assessment of prescriptions and, protocol discussions[4-5,7-8,25].

Patterns observed in our study cooperate to the design of the prevalent PDDI profile in Brazilian cardiologic units, and they demonstrate the need to develop systematic preventive actions. The presented results corroborate with other studies conducted in teaching hospitals, as the prevalence of moderate and major interactions, and the correlation between the number of prescribed drugs and the hospitalization time with the PDDI presence in prescriptions[12-14].

Another known factor in the literature, through the studies with different designs and varied sample sizes, is the relationship between the number of prescribed drugs and the number of PDDI present in prescriptions. This correlation reinforces the inherent risk to polypharmacy present in prescriptions involving a large number of drugs[1,7-8,12-14].

Because the teaching hospital of this study does not have an updated and active Clinical Pharmacy service, we did not observe the real occurrence of interactions in patients, and this is a limiting factor. Therefore, for future studies, we suggest the continuous follow-up of the research group to assess the incidence of clinical occurrences related to PDDI, through continuous actions of the Clinical Pharmacy.

CONCLUSION

There is a high rate of potential drug-drug interactions in prescriptions for elderly hospitalized due to Acute Coronary Syndrome. To treat this Syndrome and, concomitant diseases common in this age group, this patient's profile consumes drugs of different pharmacological groups, resulting in drug-drug interactions. Almost all prescriptions present at least one drug-drug interaction. Moderate and major intensity prescriptions were the most frequent, and most of them involved pharmacodynamic mechanisms.

Our study provides a significant collaboration to define the prevalence pattern of potential drug-drug interactions prevalence in a prescription for Acute Coronary Syndrome, contributing for the production and revision of strategies to identify and management through drug interventions.

We expect this study to serve as motivation for the production of more research involving this theme in teaching hospitals, and to act as a grant for the efficient implementation of the Clinical Pharmacy, once the action of clinical pharmacists contributes to reach better pharmacotherapeutic results.

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